URGENT NEED FOR FURTHER RESEARCH IN SUBCLINICAL HYPOTHYROIDISM

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A comprehensive systematic review has recommended decreasing the number of individuals who receive treatment for subclinical hypothyroidism; however, data included in the study are extremely limited for young individuals. Extrapolating data from older individuals is perhaps unwise; therefore, the onus should be on the urgent need for further research.

Decreased thyroid function is seen in subclinical hypothyroidism (SCH), which is defined by elevated TSH and normal free thyroid hormone levels and is regularly encountered by clinicians. We therefore read with interest a *BMJ* Rapid Recommendation, by Geertruida Bekkering and colleagues[1], in which the authors indicate a strong recommendation against the use of levothyroxine replacement in adults with SCH. Key caveats were that this recommendation should not apply to women who are trying to become pregnant (or who are currently pregnant), those with severe symptoms or patients with TSH levels of >20 mIU/l. This TSH threshold is somewhat higher than previous international guidelines from the American and European Thyroid Associations[2,3], which advocated treatment at TSH levels >10 mIU/l, with a trial of treatment to be considered in symptomatic individuals at lower TSH thresholds.

Given that SCH is present in up to 10% of the population, the present guidance[1] will affect a large number of people, especially females[3]. The difficulty for clinicians is that SCH has been associated with adverse cardiovascular, metabolic, mood and pregnancy outcomes, but the benefits of treatment with levothyroxine are unclear[4]. The Bekkering guidance[1] was based on a 2018 systematic review[5] of 21 randomized controlled trials in patients with SCH. While we recognize the value and the effort undertaken in these analyses[1,5], we feel it is important to moderate the conclusions regarding TSH threshold at treatment initiation.

As Bekkering and colleagues note, the studies included in the systematic review[5] were small — the 21 clinical trials studied contained only 2,192 participants. These clinical trials were varied with regard to TSH threshold required for treatment initiation and age of the participants. In addition, a third of all the patients studied in the review ($n = 737$) were from the TRUST study[6] and ~75% of the participants with quality of life assessments were from this one study. The TRUST study was originally intended to be a cardiovascular trial, and as such focused on patients >65 years old (mean age in the trial was 74.4 years). Furthermore, based on the quality of life measures used in TRUST, hypothyroid symptoms at baseline were similar to those reported in patients with hypothyroidism who had already been treated with levothyroxine. Thus, improvements in symptoms might not have been expected in this largely asymptomatic population. TSH thresholds were also modest; the baseline median TSH was 5.76 mU/l (interquartile range 5.10–6.94 mU/l) in the placebo group and 5.73 mU/l (interquartile range 5.12–6.83 mU/l) in the treatment group. Therefore, the TRUST trial provides information only on older individuals with mild SCH and symptoms.

It is increasingly recognized that increased levels of TSH might be a normal part of ageing, with the upper 97.5% confidence interval for serum levels of TSH in healthy elderly persons being ~7.5 mIU/l (ref.[7]). This important consideration does not seem to have been taken into account by the authors of this guidance[1]. Given that many individuals in the TRUST study[6] are likely to have had normal age-adjusted thyroid function, it is perhaps unsurprising that the authors of the TRUST study found no evidence of treatment benefit. Therefore, it would seem to be unwise to extrapolate these findings to individuals who are <65 years old, as in this demographic elevations in TSH are not yet within the reference range. This point is particularly important as observational data

do show increased adverse cardiovascular outcomes in SCH at TSH levels >10.0 mIU/l (ref.[8]) and there seems to be an age interaction with regard to treatment with benefits seen in those aged <65 years[9].

The guidance from Bekkering and colleagues[1] does point out that quality of life findings were similar[1] when the TRUST study was removed from analyses. However, by removing the TRUST trial, the problem now becomes lack of power. When TRUST is excluded from the review, there are only 423 participants in whom quality of life or cognition were studied, as several other studies focused on other factors such as BMI. Based on the baseline data of these studies[5], only a small proportion of these 423 participants would have an age <40 years or TSH levels >8.0 mIU/l. Furthermore, owing to the nature of the studies included, the quality of life assessments have incorporated heterogeneous measures that assess general health status, and screening tools for minor psychiatric disorders; this incorporation has both weakened the power and confidence we can have in the guidance for quality of life. Only a small number of patients with TSH levels of >10 mIU/l have been studied in a randomized manner[5] and health-care professionals should communicate the uncertainty around the data to patients rather than raising the TSH threshold to a very high threshold of 20 mIU/l.

We welcome the caveat in the present guidance, which states that the guidance should not apply to women who are pregnant or to those who are planning pregnancy. However, given that many pregnancies are unplanned, this guidance might still expose women of child-bearing age to substantial hypothyroidism and substantial hypothyroidism in early pregnancy, with clear potential for adverse obstetric and offspring outcomes. We also agree that over-treatment with levothyroxine can lead to adverse outcomes as the authors highlight, but sensible monitoring and patient education can mitigate this. It would seem logical that concerns regarding potential over-treatment should not solely prevent treatment initiation.

Taken together, we are concerned that based on the present guidance[1], treatment might be erroneously denied to symptomatic or young individuals with SCH. The caveat for severe symptoms might mitigate this, but younger individuals with TSH levels >10 mIU/l and only moderate symptoms would be denied treatment. For instance, many endocrinologists would find it very hard to justify denial of a trial of levothyroxine treatment to a symptomatic 44-year-old female with a TSH of 9.5 mIU/l or an asymptomatic 35-year-old woman with no clear pregnancy plans and a TSH of 19.0 mIU/l, although these patients would now be recommended not to receive treatment, according to this guidance. What the clearly summarized and presented systematic review[5] and guidance[1] do highlight is the paucity of high-quality evidence in this area. This lack of evidence is both surprising and highly regrettable as SCH is so common and because many patients have persistent concerns and dissatisfaction with their thyroid hormone replacement[10].

We strongly believe that a much more important conclusion from this work is that carefully conducted trials of SCH are urgently needed. Such trials need to be an order of magnitude larger than previous studies, focus on younger individuals and control for other factors, such as inter-individual genetic variation when ascertaining treatment response. In addition to TSH, other biomarkers of tissue hypothyroidism need to be identified. Further work is needed on assessing thyroid hormone replacement itself, in particular the potential role of combination thyroid hormone replacement with liothyronine and levothyroxine. Thus, urgent research action is needed, not clinical inaction.

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